Minireview

The Zinc Finger-containing Transcription Factors GATA-4, -5, and -6

UBIQUITOUSLY EXPRESSED REGULATORS OF TISSUE-SPECIFIC GENE EXPRESSION*

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Six GATA transcription factors have been identified in vertebrates, each of which contains a highly conserved DNA binding domain consisting of two zinc fingers of the motif $Cys-X_2-Cys-X_{17}-Cys-X_2-Cys$ (1–9) that directs binding to the nucleotide sequence element (A/T)GATA(A/G) (10, 11). Based on their expression patterns, the GATA proteins have been divided into two subfamilies, GATA-1, -2, and -3 and GATA-4, -5, and -6. *GATA-1, -2,* and *-3* genes are prominently expressed in hematopoietic stem cells where they regulate differentiation-specific gene expression in T-lymphocytes, erythroid cells, and megakaryocytes (reviewed in Ref. 12). *GATA-4, -5,* and *-6* genes are expressed in various mesoderm- and endoderm-derived tissues such as heart, liver, lung, gonad, and gut where they play critical roles in regulating tissue-specific gene expression (4–9). Consistent with the observed expression patterns for GATA-4, -5, and -6, targeted disruption of each gene in the mouse has revealed important functions in heart, endoderm, lung epithelium, and genitourinary tract formation. Here we will discuss the biochemical characteristics and transcriptional regulatory roles of GATA-4, -5, and -6 transcription factors.

Structure-Function Analysis of GATA-4, -5, and -6 Proteins

The mouse *GATA-4, -5,* and *-6* genes encode proteins of 48, 42, and 45 kDa, respectively (4, 7, 8). Each protein contains a highly conserved DNA binding domain that consists of two zinc finger motifs and two adjacent stretches of basic amino acids (Fig. 1, *A* and *B*). GATA-4, -5, and -6 are ~85% identical to one another at the amino acid level within the DNA binding region containing the zinc finger and basic regions (Fig. 1B). Furthermore, mouse *GATA-4* is ~70% identical to mouse *GATA-1* and *Drosophila pannier* within the DNA binding region, suggesting a high degree of sequence conservation between divergent GATA family members and across evolutionary disparate organisms (Fig. 1A).

Given the high degree of sequence identity between GATA protein family members, predictions can be drawn as to the residues that mediate DNA binding in GATA-4, -5, and -6 based on structural and mutagenesis studies performed in GATA-1. A number of reports have demonstrated that only the C-terminal zinc finger and adjacent basic domain are necessary for specific DNA binding *in vitro* (13–15). Using NMR, GATA-1 was shown to interact with 8 nucleotide base pairs when bound to DNA such that the N-terminal and central portion of the GATA-1 DNA binding domain made specific contacts within the major groove, whereas the C-terminal portion made site-specific interactions within the minor groove

(13). Whereas just the C-terminal finger of GATA-1 is required for specific DNA binding, the N-terminal finger can interact with adjacent GATA DNA sequence elements or with protein cofactors (16, 17). Protein domain deletion analysis of GATA-4 confirms that the C-terminal zinc finger is necessary and sufficient for DNA binding, as with GATA-1 (18).

The nuclear localization and transcriptional activation domains of GATA-4 have also been identified (18). Deletion analysis suggests that a strong nuclear localization sequence is present within the basic domain adjacent to the C-terminal finger (amino acids 251–324), whereas two separate transcriptional activation domains are present within the N terminus of the protein (18) (Fig. 1A). Interestingly these transcriptional activation domains are partially conserved in GATA-5 and -6, suggesting a similar mechanism of transcriptional activation within the GATA-4, -5, and -6 subfamily (18). However, a naturally occurring splice variant of GATA-5 lacking the N-terminal activation domain still promotes modest transcriptional activation suggesting the presence of a weak transcriptional activation domain in the C terminus of GATA-5 (19).

Using polymerase chain reaction site selection, GATA-1, -2, and -3 were each determined to bind the DNA consensus site (A/T)GATA(A/G), whereas GATA-2 and GATA-3 were also capable of binding the GATA-like site AGATCTT (10, 11). Characterization of the 5'-regulatory regions of numerous genes has demonstrated that GATA-4, -5, and -6 factors also interact with a DNA sequence element containing a core GATA motif. More recently, polymerase chain reaction site selection with GATA-6 protein demonstrated an order of site preference to be GATA>GATT>GATC (20). These analyses suggest that although GATA factors universally recognize a GATA DNA sequence element, subtle differences in the GATA core DNA motif might promote differential binding among coexpressed GATA family members within a specific tissue. Indeed, GATA-4, but not GATA-2 or GATA-3, specifically regulates expression of the interleukin-5 gene in a human T-cell line (21). In addition, activation of the α- and β-myosin heavy chain promoters preferentially utilized GATA-4 over GATA-6 in cardiac myocytes (22). Finally, the promoter of the novel phosphoprotein gene *Dab2* was regulated by GATA-6, but not GATA-4, in visceral endoderm (23). Collectively, these studies indicate that although GATA-4, -5, and -6 each bind a GATA or GATA-like sequence element, their individual affinities for various promoters might depend on flanking nucleotide sequences or even on interactions with cofactors and other transcription factors. Such interactions might also provide a complex transcriptional code that allows programming of tissue-specific gene expression, despite a relatively broad expression pattern in multiple mesodermal and endodermal derived tissues.

Expression Patterns and Gene Targeting in the Mouse

In the adult mouse, GATA-4 mRNA is detected in the heart, ovary, testis, lung, liver, and small intestine (4). In embryonic and fetal mice, *GATA-4* is expressed in the heart, proximal and distal gut, testis, ovary, liver, visceral endoderm, and parietal endoderm (4, 7). *GATA-5* gene is expressed in the adult small intestine, stomach, bladder, and lungs whereas developmentally expression is detected in the allantois, heart, outflow tract, lung bud, urogenital ridge, bladder, and gut epithelium (8). Finally, mouse *GATA-6* is expressed in the adult heart, aorta, stomach, small intestine, and bladder and weakly in the liver and lung (7). During embryonic and fetal development, GATA-6 mRNA is detected in the primitive streak, allantois, visceral endoderm, heart, lung buds, urogenital ridge, vascular smooth muscle cells, and the epithelial layer of the stomach, small intestine, and large intestine (7, 9, 24, 25). Collectively, these studies indicate that most tissues of either mesodermal or endodermal origin express one or more GATA-4, -5, or -6 factors at some point during development. Given these characteristic broad fields of expression one might predict that GATA-4, -5,
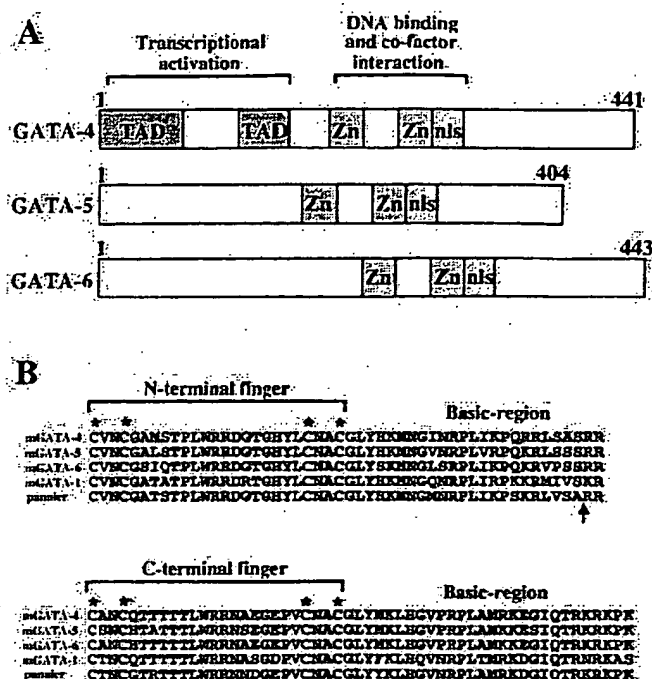
FIG. 1. **Structural domains and amino acid sequences of GATA-4, -5, and -6 transcription factors.** *A*, GATA-4 contains two distinct zinc finger domains (*Zn*) and a C-terminal nuclear localization sequence (*nls*) that together constitute the DNA binding and protein-protein interaction domain. GATA-4 also contains two transcriptional activation domains (*TAD*) in the N terminus. *B*, amino acid sequence of the two zinc finger domains and the adjacent basic regions. Mouse GATA-1 and *D. pannier* amino acid sequences are also shown for comparison. The *blue shaded region* represents identity to GATA-4 (consensus) whereas *unshaded areas* represent differences in amino acid sequence. The *asterisk* shows the cysteines that generate each zinc finger subdomain, whereas the *arrow* denotes the position of a 3-amino acid insertion (sequence not shown) that is uniquely present in *pannier*.

and -6 factors are unlikely to act as master regulators of cell type specificity or determination. For example, the MyoD family of basic helix-loop-helix transcription factors is exclusively expressed in skeletal muscle, where they act as master regulators of myoblast cell identity and differentiation. However, it remains possible that GATA-4, -5, and -6 might still serve a function in regulating cell type specification or determination through unique interactions with other semi-restricted transcription factors. Such a notion is also consistent with the observed role of GATA-1, -2, and -3 as master regulators of erythroid and lymphoid cell identity, despite the observation that each factor is expressed outside hematopoietic cell lineages (12).

Targeted disruption of the *GATA-4, -5,* and *-6* genes in the mouse has revealed phenotypes consistent with their individual expression patterns. Mice null for *GATA-4* die between embryonic day 8 and 9 because of defects in heart morphogenesis and ventral closure of the foregut (26, 27). Specifically, *GATA-4* null mice present with cardia bifida because of ineffective ventral fusion of the lateral aspects of the embryo and the subsequent formation of the foregut. Aberrant heart formation in *GATA-4* null mice is likely a secondary effect associated with an intrinsic defect in the definitive endoderm that underlies the splanchnic mesoderm containing the cardiac field (28). This interpretation is further supported by the observation that *GATA-4* null embryonic stem cells can generate cardiac myocytes but are partially defective in their ability to generate visceral endoderm and definitive endoderm of the foregut (27, 29, 30). Finally, a role for GATA-4 in heart development is further suggested by the identification of a deletion in human chromosome 8p23.1 that contains the *GATA-4* gene and is associated with congenital heart disease (31, 32). Taken together, it is likely that GATA-4 regulates cardiac development by both direct and indirect mechanisms.

Targeted disruption of the *GATA-5* gene in the mouse did not result in developmental lethality but instead females displayed defects in genitourinary tract development (33), consistent with the observed pattern of *GATA-5* expression in the urogenital ridge

during embryogenesis (8). Interestingly, a *GATA-5* null mutation in zebrafish resulted in embryonic lethality with an identical phenotype to that observed in *GATA-4* null mice, suggesting a reversal in the roles of *GATA-4* and *GATA-5* between the mouse and fish (34). *GATA-6* null mice die during early embryonic development (embryonic day 5.5–7.5) because of defects in visceral endoderm function and subsequent extraembryonic development (35, 36), a phenotype that is consistent with the expression pattern of *GATA-6* in the embryonic primitive endoderm (7). In the future, it will be interesting to generate tissue-specific disruptions of GATA-4 and -6 in the mouse using cre-lox technology to permit a more careful evaluation of the role that each factor plays in regulating of tissue-specific gene expression in the heart, gut, lung, and liver.

Expression of *GATA-4* and *-6* is dependent on one another given the observation that *GATA-6* is up-regulated in *GATA-4* null mice and that *GATA-6* null embryos show down-regulation of *GATA-4* (26, 27, 36). Although the mechanism underlying this regulation has not been elucidated, it is tempting to speculate that GATA-4 negatively regulates GATA-6 gene expression whereas GATA-6 positively regulates GATA-4 gene expression. Such a transcriptional interconnection between GATA-4 and GATA-6 is also consistent with the observations that *GATA-4* and *-6* double heterozygous mice are nonviable and die during embryonic development.[1] Alternatively, it is also possible that the absolute dosage of GATA-4 and -6 proteins is critical for proper development. An interdependence between these two transcription factors is also supported by the observation that GATA-4 and -6 proteins colocalize with one another in the nucleus of cardiac myocytes and form stable dimeric complexes (22).

Role of GATA-4, -5, and -6 in Tissue-specific Gene Expression

GATA-4, -5, and -6 have been implicated as important regulators of gene expression in heart, liver, gonad, gut epithelium, and lung. GATA-4 regulates expression of a number of cardiac structural genes such as α-myosin heavy chain, cardiac troponin-C, atrial natriuretic factor and brain natriuretic peptide, cardiac troponin-I, sodium/calcium exchanger, cardiac restricted ankyrin repeat protein, A1 adenosine receptor, m2 muscarinic receptor, and the myosin light chain 1/3 (37–49). GATA factors also regulate developmental expression of the cardiac transcription factor Nkx2.5, suggesting the existence of a reinforcing transcriptional regulatory circuit between Nkx2.5 and GATA factors in the heart (50, 51). Furthermore, the *Drosophila* GATA factor, *pannier*, regulates expression of the myocyte enhancer factor-2 (MEF-2)[2] gene in cardioblasts, extending the role of GATA factors as regulators of heart gene expression to include invertebrates (52). Collectively, the studies discussed above indicate that GATA factors are important regulators of both structural and regulatory genes in the heart.

GATA-6 has been implicated in the transcriptional regulation of genes within the respiratory epithelium of the lung. Specifically, GATA-6 regulates expression of the surfactant protein A and thyroid transcription factor-1 (TTF-1) promoters (53, 54). Interestingly, GATA-5 was unable to regulate TTF-1 promoter activity, suggesting a specific role for GATA-6 in the lung (54). That GATA-6 is an important lung-determining factor is further supported by the observation that *GATA-6* null embryonic stem cells fail to contribute to the lung epithelium in chimeric mouse embryos (36).

GATA-4, -5, and -6 have also been implicated in the regulation of epithelial cell differentiation in the gut, where they regulate expression of the H^{+}/K^{+}-ATPase and the trefoil factor family promoters (55–58). GATA proteins are also required for efficient gene expression in the gut of *Caenorhabditis elegans*, suggesting an evolutionary conserved role for GATA factors in gut development between vertebrates and invertebrates (59).

GATA-4 and -6 have also been implicated in the regulation of liver-specific gene expression through analysis of the albumin promoter, vitellogenin II promoter, and the liver-enriched homeobox gene promoter, Hex (60–62). GATA-4, -5, and -6 factors are also

important regulators of gene expression within the gonads. Expression of the Mullerian inhibiting substance promoter is regulated by GATA-4 in Sertoli cells and Mullerian ducts (63–65), and GATA-4 regulates expression of the steroidogenic acute regulatory protein promoter in the ovary (66). Collectively, these various studies indicate that GATA-4, -5, and -6 factors are important regulators of tissue-specific gene expression in multiple endoderm- and mesoderm-derived tissues. However, it is likely that GATA-4, -5, and -6 factors regulate tissue-specific gene expression across these divergent cell types through specific interactions with other semi-restricted transcription factors or cofactors (see below).

GATA-4, -5, and -6 Regulate Inducible Gene Expression

GATA-4 has been implicated as a regulator of inducible gene expression in cardiac myocytes in response to hypertrophic stimulation. Specifically, analysis of the β-myosin heavy chain promoter in aortic-banded rats (pressure overload) revealed a proximal GATA binding site that directed hypertrophy-responsive gene expression (67). In a similar approach, GATA-4 was implicated as a regulator of angiotensin type-1A receptor promoter in response to pressure overload stimulation in the adult rat heart (68). In cultured neonatal cardiomyocytes, electrical pacing-induced hypertrophy was associated with a significant increase in GATA-4 mRNA, suggesting a mechanism of regulation whereby total GATA-4 content is up-regulated during hypertrophy (69). Alternatively, GATA-4 transcriptional activity might also be regulated by phosphorylation mediated by extracellular signal-regulated kinase in response to hypertrophic agonist administration (70). Finally, GATA-5 was shown to mediate leukemia inhibitory factor-induced expression of the β-myosin heavy chain promoter in cultured cardiomyocytes (71). Collectively, these various reports implicate GATA transcription factors as important regulators of hypertrophy-associated gene expression in cardiomyocytes. Evidence suggests that both transcriptional and post-transcriptional mechanisms are involved in augmenting GATA-4 potency during hypertrophy in cardiac myocytes.

Analysis of vascular smooth muscle cells has demonstrated an important role for GATA-6 in regulating cell proliferation in response to mitogenic or mechanical stimulation. GATA-6 mRNA levels are down-regulated in proliferating vascular smooth muscle cells, suggesting that GATA-6 expression is linked to the cell cycle in these cells (9). More specifically, forced expression of GATA-6 in vascular smooth muscle cells induced growth arrest through a mechanism involving enhanced expression of the cyclin-dependent kinase inhibitor p21 (72). In vivo, adenovirus-mediated gene transfer of GATA-6 in balloon-injured carotid arteries prevented vessel lesions associated with vascular smooth muscle cell phenotypic modulation (73). These studies suggest that GATA-6 is an important regulator of vascular smooth muscle cell proliferation and subsequent vascular injury. It will be of interest to determine whether GATA-6 controls cell cycle arrest in other cell types in which it is expressed or if such regulation is unique to vascular smooth muscle cells.

GATA-4, -5, and -6 Interacting Factors

A vast array of GATA-4, -5, and -6 interacting proteins has been described, including both DNA binding factors and general transcriptional activators and repressors. It is likely that such a wide array of interacting factors reflects transcriptional mechanisms whereby tissue-specific gene expression is orchestrated across various mesodermal and endodermal cell types. In the heart, GATA-4 directly interacts with the transcription factor Nkx2.5 to regulate expression of the atrial natriuretic factor and cardiac α-actin promoter (74–76). This interaction is mediated by the C-terminal zinc finger domain of GATA-4 and helix III of the homeodomain of Nkx2.5 (74–76). GATA-4 also physically interacts by way of the C-terminal zinc finger with nuclear factor of activated T-cells-c4 (NFATc4) and MEF-2 in the regulation of cardiac gene expression (77, 78). Such results suggest a paradigm whereby GATA-4 regulates heart-specific gene expression through complexes with other heart-expressed transcription factors. In Sertoli cells, GATA-4 was shown to physically interact with the nuclear receptor, SF-1, leading to transcriptional synergy on the Mullerian inhibiting substance gene promoter (63). Finally, GATA-4 and -6 were shown to
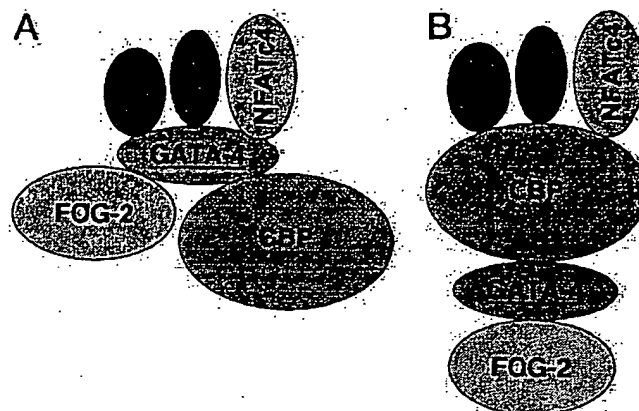

FIG. 2. **Two models of GATA-4 transcriptional complexes that could regulate cardiac gene expression.** A, the C-terminal zinc finger domain of GATA-4 may directly interact with the transcription factors Nkx2.5, NFATc4, and MEF2 as well as CBP, whereas FOG-2 interacts with the N-terminal zinc finger. It is uncertain if GATA-4 can interact with each of these factors at the same time or if interaction with one precludes further interactions. B, alternatively, GATA-4 may indirectly interact with Nkx2.5, NFATc4, and MEF2 through a mutual association with CBP (or p300).

physically interact with one another in cardiac myocytes suggesting heterodimerization between GATA factors (22).

It is uncertain how the C-terminal zinc finger domain of GATA-4 is capable of mediating interactions with such a broad array of disparate transcription factors, especially because this same protein domain makes direct nucleotide contacts within the major groove of DNA. Despite this concern, it is formally possible that GATA-4 directly interacts with each of the characterized transcription factors as part of a cell type-specific complex (Fig. 2A). However, it is also possible that GATA-4 exists as a heterogenous pool consisting of only one or a few of these cofactors at any one time. Alternatively, GATA-4 may exist as a large complex with other transcription factors through an indirect association with general regulators of transcription such as p300/CBP (Fig. 2B). Consistent with this hypothesis, GATA-5 and -6 were each shown to physically interact with p300 resulting in transcriptional synergy (79, 80), and CBP was reported to stimulate transcription dependent on GATA-4 (81). More recently, GATA-4 was shown to interact with the transcriptional modifying protein, friend of GATA-2 (FOG-2), through a physical interaction involving the N-terminal zinc finger of GATA-4 (82–84). This interaction is conserved in Drosophila where the FOG-2 homologue, U-shaped, interacts with pannier, a GATA homologue (85). It is likely that FOG-2 plays an important role in regulating GATA factor-dependent gene expression in the heart given the phenotype of FOG-2 knock-out mice that die during embryogenesis with significant cardiac abnormalities (86, 87). It is uncertain if FOG-2 acts as a general transcriptional activator or repressor of GATA-4, -5, and -6 factors or if transcriptional modifying activity varies from cell type to cell type. However, FOG-2 also interacts with the transcriptional repressor protein, CtBP2, implicating FOG-2 as a general transcriptional repressor of GATA-4, -5, and -6 activity (88).

Model of GATA-4, -5, and -6 as Tissue-unrestricted Enhancer Factors

Whereas the majority of studies pertaining to GATA-4, -5, and -6 transcription factors have focused on cardiac expressed genes, recent evidence indicates that multiple tissues utilize GATA-4, -5, or -6 factors in programming cell type-specific gene expression. However, it is uncertain how a family of widely expressed transcription factors might regulate differentiation-specific gene expression and tissue identity in such diverse cell types as heart, lung, and liver. Tissue specificity afforded by GATA-4, -5, or -6 transcription factors may arise through cell type-specific interactions with other transcription factors that themselves are expressed in semi-restricted patterns. For example, GATA-4 physically interacts with the transcription factors Nkx2.5, MEF-2, and NFATc4, which together are coexpressed uniquely in the myocardium. In the lung, GATA-6 physically interacts with the semi-restricted homeobox factor TTF-1, suggesting a unique combinatorial transcriptional

code that is specific to the lung. In conclusion, numerous studies have established a paradigm whereby the subfamily of GATA-4, -5, and -6 factors regulates tissue-specific gene expression in multiple cell types through unique interactions with other semi-restricted transcription factors.

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